

Atty. Dkt. No.: 32892.19
USSN: Unassigned
Inventor: Eugenio A. Cefali

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U.S.P.T.O.
JC519

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

EUGENIO A. CEFALI

Entitled: Methods for Treating Hyperlipidemia With Intermediate Release Nicotinic Acid Compositions Having Unique Biopharmaceutical Characteristics

To the Assistant Commissioner
for Patents
Box Patent Application
Washington, D.C. 20231

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Dear Sir:

REQUEST FOR FILING A NATIONAL PATENT APPLICATION

Transmitted herewith for filing, please find the following:

- i. Specification, claims and abstract of the above-referenced patent application having 52 pages.
- ii. Drawings (formal / informal) comprising Figures 1-5.
- iii. Combined Declaration and Power of Attorneys
(signed unsigned).
- 3A. No executed Oath, or Declaration, nor is any fee enclosed pursuant to 37 C.F.R 1.53(d).
- iv. Information Disclosure Statement along with Form PTO-1449 and references.

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v. This is a: Continuation-In-Part; Divisional; Continuation; substitute Application (MPEP 201.09) of Application Serial No. 08/814,974 filed March 6, 1997; reissue of U.S. Patent No. filed on .

An extension to extend the life of the above prior Application to at least the date of filing hereof

(One box must be marked)

(a) _____ is concurrently being filed in that prior Application,
(b) _____ was previously filed in that prior Application,
(c) X is not necessary for copendency.

vi. Attached is an assignment to _____ . Please return the recorded assignment to the undersigned.

vii. Priority is claimed under 35 U.S.C. § 119 based on filing in (country).

Application No. Filing Date

(1)	_____	_____
(2)	_____	_____
(3)	_____	_____

(No.) Certified copy (copies) are attached; or were previously filed on .

viii. Attached: ____ (No.) verified statement(s) establishing "small entity" status under 37 CFR § 1.9 and 1.27.

X ix. Attached:

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 Assignment (unsigned)
 Verified Statement (unsigned)

x. **Preliminary Amendment:**

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Prior to a first Office Action, kindly amend the Application as follows:

xi. The following Filing Fee calculation is based on the claims filed less any claims canceled by the Preliminary Amendment of Item 10.

				SMALL ENTITY RATE		LARGE ENTITY RATE		
BASIC FEE				\$ 395.00	<u>OR</u>	\$	=	+\$ 395.00
	NUMBER FILED		NUMBER EXTRA					
TOTAL CLAIMS	27	-20	=	7 (at least 0)	x 11	<u>OR</u>	x 22	= +\$ 77.00
INDEP. CLAIMS	2	- 3	=	0 (at least 0)	x 40	<u>OR</u>	x 80	= +\$
If any <u>proper</u> multiple dependent claim (ignore improper) is present (Enter \$0.00 if this is a <u>reissue</u> application.)				+\$130	<u>OR</u>	+\$260	=	+\$
If assignment is x'd (item 6), add recording fee \$40.00								+\$
Attached is a Rule 47 Petition (inventor refuses to sign or cannot be reached) \$130								+\$
TOTAL FILING FEE								=\$ 472.00

— xii. A check in the amount of \$ _____ to cover the Filing Fee calculated in Item 11 is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0447/32892.18.

— xiii. Please charge my Deposit Account No. 10-0447 in the amount of \$ _____ to cover the Filing Fee calculated in Item 11. This sheet is attached in duplicate.

— xiv. The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and may be required under 37 CFR 1.16-1.18 (missing or insufficiencies only) now or hereafter

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relative to this application and for the resulting Official Document under 37 CFR 1.20, and to have and cause any necessary petition for extension of time to be filed and any fees necessary to be paid for said extension of time OR credit any overpayment to our Deposit Account No. 10-0447, for which purpose a duplicate copy of this sheet is attached. The Commissioner is not authorized to charge the issue fee until/unless an issue fee transmittal form is filed.

Respectfully submitted,

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**METHODS FOR TREATING
HYPERLIPIDEMIA WITH INTERMEDIATE RELEASE NICOTINIC ACID
COMPOSITIONS HAVING UNIQUE BIOPHARMACEUTICAL CHARACTERISTICS**

Related Patent Applications

This application for U.S. patent is a U.S.C., Title 35, §111(a) application, which is a continuation-in-part of U.S. Patent Application, Serial No. 08/814,974 filed March 6, 1997.

Field of the Invention

The present invention is directed to intermediate release nicotinic acid formulations useful for treating hyperlipidemia and methods of treating hyperlipidemia employing such compositions. Another aspect of the present invention, the nicotinic acid formulations are suitable for once a day dosing without causing drug-induced hepatotoxicity to a level which would require the therapy to be discontinued. More particularly, the present invention employs a composition of nicotinic acid, derivatives and mixtures thereof, and a swelling agent to form an intermediate timed-release sustaining composition for nocturnal or evening dosing. Specifically, the present invention employs a composition of nicotinic acid and hydroxypropyl methylcellulose to treat hyperlipidemia in a once per day oral dosage form given during the evening hours that causes little if any hepatotoxicity.

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Background

Nicotinic acid, 3-pyridinecarboxylic acid or niacin, is an antilipidemic agent that is marketed under, for example, the trade names Nicolar®, SloNiacin®, Nicobid® and Time Release Niacin®. Nicotinic acid has been used for many years in the treatment of lipidemic disorders such as hyperlipidemia, hypercholesterolemia and atherosclerosis. This compound has long been known to

exhibit the beneficial effects of reducing total cholesterol, low density lipoproteins or "LDL cholesterol," triglycerides and apolipoprotein a (Lp(a)) in the human body, while increasing desirable high density lipoproteins or "HDL cholesterol".

Typical doses range from about 1 gram to about 3 grams daily. Nicotinic acid is normally administered two to four times per day after meals, depending upon the dosage form selected. 5 Nicotinic acid is currently commercially available in two dosage forms. One dosage form is an immediate or rapid release tablet which should be administered three or four times per day. Immediate release ("IR") nicotinic acid formulations generally release nearly all of their nicotinic acid within about 30 to 60 minutes following ingestion, as illustrated in Fig. 1. The other dosage form is a sustained release form which is suitable for administration two to four times per day. See, however, U.S. Patent No. 5,126,145 issued to O'Neill. In contrast to IR formulations, sustained release ("SR") nicotinic acid formulations are designed to release significant quantities of drug for absorption into the blood stream over specific timed intervals, also as shown in Fig. 1. If the release occurs at appropriate times, therapeutic levels will be maintained by SR nicotinic acid formulations over an extended period such as 12 or 24 hours after ingestion.

10 The dosing regimen of IR nicotinic acid is known to provide a very beneficial effect on blood lipids as discussed in Knopp *et al.*; "Contrasting Effects of Unmodified and Time-Release Forms of Niacin on Lipoproteins in Hyperlipidemic Subjects: Clues to Mechanism of Action of Niacin"; Metabolism 34/7, 1985, page 647. The chief advantage of this profile is the ability of IR nicotinic acid to decrease total cholesterol, LDL cholesterol, triglycerides and Lp(a) while increasing HDL 15 particles. In fact, IR nicotinic acid has been well regarded as an effective drug in the treatment of high cholesterol since about the early 1960s. Unfortunately, IR nicotinic acid has never really become widely used because of the high incidence of flush that often occurs when an IR dose is taken. That means an individual may develop a visible, uncomfortable, hot or flushed feeling three or four times a day for about one hour following each IR dose.

20 25 In order to avoid or reduce the cutaneous flushing, a number of materials have been suggested for administration with an effective antihyperlipidemic amount of immediate release nicotinic acid,

including guar gum in U.S. Patent No. 4,956,252, and mineral salts as disclosed in U.S. Patent No. 5,023,245; or inorganic magnesium salts as reported in U.S. Patent No. 4,911,917. These materials have been reported to avoid or reduce the cutaneous flushing side effect commonly associated with nicotinic acid treatment.

Another method of avoiding or reducing the side effects associated with immediate release 5 nicotinic acid is the use of SR nicotinic acid formulations. SR nicotinic acid formulations are designed to slowly release the compound from the tablet or capsule. The slow drug release reduces and prolongs blood levels of drug in an attempt to lower peak nicotinic acid concentrations with the goal of reducing or eliminating nicotinic acid induced flush. Examples of currently marketed SR formulations of nicotinic acid include Nicobid® capsules (Rhone-Poulenc Rorer), Enduracin® (Innovative Corporation) and SloNiacin® (Upsher-Smith Laboratories, Inc., U.S. Patent. No. 5,126,145, which describes a sustained release niacin formulation containing two different types of hydroxypropyl methylcellulose and a hydrophobic component).

Studies in hyperlipidemic patients have been conducted with a number of SR nicotinic acid products. These studies have demonstrated that the sustained release products do not have the same 10 advantageous lipid altering effects as IR nicotinic acid, and in fact often have a worse side effect profile compared to the IR products. The major disadvantage of the SR formulations, as can be seen in Knopp *et al.*, in 1985, is the significantly lower reduction in triglycerides (-2% for the sustained release versus -38% for the immediate release) and lower increase in HDL cholesterol, represented 15 as HDL₂ particles which are known by the art to be most beneficial, (-5% for the sustained release versus +37% for the immediate release).

Additionally, SR nicotinic acid formulations have been noted as causing greater incidences 20 of liver toxicity as described in Henken *et al.*: Am J Med, 91:1991 (1991) and Dalton *et al.*: Am J Med, 93:102 (1992). There is also great concern regarding the potential of these formulations in disrupting glucose metabolism and uric acid levels.

In a recent edition of the Journal of the American Medical Association, an article appeared 25 which presented research results investigating the liver toxicity problems associated with an SR form

of nicotinic acid. See McKenney *et al.*: A Comparison of the Efficacy and Toxic Effects of Sustained- vs. Immediate-Release Niacin in Hypercholesterolemic Patients, JAMA, (271)9: 672 (March 2, 1994). This McKenney *et al.* article presented a study of twenty-three patients. Of that number, 18 or 78 percent were forced to withdraw because liver function tests (LFTs) increased indicating potential liver damage. The conclusion of the authors of that article was that the SR form of nicotinic acid "should be restricted from use."

A similar conclusion was reached in an article authored by representatives of the Food and Drug Administration. See Radar, *et al.*: Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin, JAMA, 267:77 (January 1992). Because of these studies and similar conclusions drawn by other health care professionals, the sustained release forms of nicotinic acid have experienced limited utilization.

Consistent with these conclusions, certain IR formulations are FDA approved for the treatment of hyperlipidemia. The SR products, however, are not FDA approved for the treatment of hyperlipidemia and may only be marketed as over-the-counter nutritional supplies. As over-the-counter nutritional supplements, SR nicotinic acid formulations are not subject to the rigorous FDA imposed *in vivo* and *in vitro* testing required of prescription SR products. Rather, anyone can market an SR nicotinic acid product as a nutritional supplement as long as it is manufactured using "Good Manufacturing Procedures." Notwithstanding their commercial availability in the United States, many investigators have recommended that the SR nicotinic acid products be removed from non-prescription status because of their incidence of hepatotoxicity and the lack of sufficient medical testing to support their marketing. See Dalton, T.A. *et al.*: Am J Med, (93):102-104 (1992); Etchason, J.A. *et al.*: Mayo Clin Proc, (66):23-28 (1991); and Fischer, D.J. *et al.*: Western J. Med., (155)4:410-412 (1991).

In designing an SR nicotinic acid product, the pharmacokinetics can have a considerable impact on whether a particular SR nicotinic acid will produce satisfactory results after *in vivo* administration. Orally administered drugs, such as nicotinic acid, are absorbed and enter the capillaries and veins of the upper GI tract and are transported by the portal vein directly to the liver

before entering the general circulation of the body. The entire absorbed drug is exposed to the liver during its first pass through the body. If a drug is subject to a high hepatic clearance, i.e., it is rapidly metabolized by the liver, then a substantial fraction of the absorbed dose is extracted from the blood and metabolized before it reaches the systemic circulation. This phenomenon is characterized as the “first pass effect.” The consequence of this phenomenon is a significant reduction in bioavailability.

5 In some instances, the first pass effect is so large as to render oral administration of a drug ineffective.

The pharmacokinetics of nicotinic acid have been somewhat studied in the past. Nicotinic acid is well absorbed from the gastrointestinal tract and is subjected to an extensive first pass effect. More particularly, nicotinic acid is metabolized into many products as depicted in Fig. 2 and undergoes saturable first pass metabolism resulting into two metabolic pathways. Pathway 2 is the saturable pathway, whereas Pathway 1 is the secondary metabolic process that is initiated only after all of the enzymes in Pathway 2 are occupied or “saturated.” In other words, as the concentration of nicotinic acid accumulates or backs up due to the “saturation” of the enzymes in Pathway 2, the secondary metabolic process, i.e., Pathway 1, is initiated. The nicotinic acid metabolites produced in both pathways are common to all nicotinic acid formulations either IR or SR. As shown in Fig. 2, Pathway 1 includes nicotinic acid and nicotinuric acid (“NUA”), and Pathway 2 includes the phase I metabolites, nicotinamide (“NAM”), 6-hydroxy nicotinamide (“6HN”), nicotinamide-N-oxide (“MNO”), N-methyl-nicotinamide (“MNA”) and nicotinamide adenine dinucleotide (“NAD”). As further shown in Fig. 2, Pathway 2 includes the metabolites of MNA, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY), and the entire NAD cycle which is necessary in nearly all biochemical processes within the cells.

20 Compounds such as nicotinic acid which are subject to a first pass metabolism are considered to have non-linear pharmacokinetics. An increase or decrease in the dose administered will not necessarily produce the corresponding increase or decrease in observed blood levels. This is believed to be dependent upon whether the metabolic level of the liver has been exceeded. Therefore, it is thought that the percent of administered nicotinic acid dose metabolized before the compound leaves the liver is dependent upon the dose administered and the release rate.

It has been long appreciated by those of skill in the art that it can be difficult to design SR formulations for compounds, like nicotinic acid, that are subjected to the first pass effect. See Urquhart et al.: Controlled-Release Pharmaceuticals, Am Pharm Assoc, (1979). Whereas an IR product allows saturation of the enzymes and a significant increase in blood levels, an SR product releasing similar quantities of drug at a slow rate will typically either not produce saturation of the primary metabolic pathway or only initiate the secondary metabolic process to a minimal extent. Consequently, a larger percentage of an SR dose will be metabolized before it has had an opportunity to clear the liver. Moreover, the particular time at which a drug should be released varies significantly with each drug and is dependent upon its pharmacokinetics. The difficulty of correctly predicting an appropriate release pattern is well known to those skilled in this art.

Therefore, it would be a valuable contribution to the art to develop an extended release nicotinic acid formulation for once a day nocturnal administration for approval by the FDA which would provide hyperlipidemic individuals with "balanced lipid alteration," i.e., reductions in total cholesterol, LDL cholesterol, triglycerides and Lp(a) as well as increases in HDL particles, with an acceptable safety profile, especially as regards to liver toxicity and effects on glucose metabolism and uric acid levels.

Summary of the Invention

In brief, the present invention alleviates and overcomes certain of the above-identified problems and shortcomings of the present state of nicotinic acid therapy through the discovery of novel nicotinic acid formulations and methods of treatment.

Generally speaking, novel nicotinic acid formulations have been discovered that optimize blood levels of nicotinic acid over a period of about 5 to about 9 hours when administered as a single oral dose for achieving a balanced lipid alteration in individuals at a time when the rate of serum lipids, lipoproteins, cholesterol and cholesterol precursor biosynthesis is believed to be at its highest. In other words, the novel nicotinic acid formulations have been uniquely formulated for administration as a single dose, preferably during the evening or at night when the nicotinic acid levels

subsequently achieved are effective for substantially lowering the levels of total cholesterol, LDL cholesterol, triglycerides and/or Lp(a) as well as raising the levels of HDL particles, all of which are primarily nocturnally synthesized. Preferably, the nicotinic acid formulations are administered at or after an evening meal or low fat snack but before bedtime, i.e., between about 6 pm and 12 am, preferably between about 8 pm and 12 am, and most preferably between about 8pm and 10pm.

5 The amount of nicotinic acid that is administered is effective to substantially lower at least one serum lipid, such as total cholesterol, LDL cholesterol, triglycerides, and/or Lp(a) and elevated HDL-C, without causing drug-induced hepatotoxicity to levels which would require the therapy to be discontinued. In other words, a single 1 to 3 gram dose of a nicotinic acid formulation of the present invention administered between about 6 pm and 12 am is believed to be as effective as an equal or higher daily dosage of nicotinic acid administered in two to four divided doses between, e.g., 8 am and 8 pm.

10 Furthermore, because at least the majority of the nicotinic acid is released and metabolized *in vivo* during a limited predetermined period of time of about 5 to about 9 hours, the liver is not being exposed to constant levels of nicotinic acid which results during the administration of long-term, spaced daily doses of SR nicotinic acid. Thus, it is believed that the nicotinic acid formulations of the present invention are unlikely to cause individuals to develop dose-limiting hepatotoxicity when used as a single daily dose administered in a therapeutic amount.

15 The nicotinic acid formulations in accordance with the present invention have been uniquely designed as intermediate release formulations which can be characterized by one or more of the following biopharmaceutic characteristics: (1) an *in vivo* stair-stepped or sigmoidal-shaped absorption profile when the plasma nicotinic acid or NUA data is deconvoluted using the Wagner-Nelson method; (2) an *in vitro* dissolution profile; (3) a fit factor F_2 ; (4) urine metabolite recovery; (5) AUC; (6) Cmax; and/or (7) Tmax. By the term "intermediate release," it is used herein to characterize the nicotinic acid formulations of the present invention which release their medication *in vitro* or *in vivo* over a period of time which is greater than about 1 to 2 hours, i.e., slower than IR niacin, but less than about 10 to 24 hours, i.e., faster than SR niacin.

It is therefore, an object of the present invention to provide a composition of nicotinic acid or any compound which is metabolized by the body to form nicotinic acid for treating hyperlipidemia.

It is another object of the present invention to provide a composition as above, which as a time release sustaining characteristic.

It is yet another object of the present invention to provide a method for employing a 5 composition as above, for treating hyperlipidemia, which results in little or no liver damage.

At least one or more of the foregoing objects, together with the advantages thereof over the known art relating to the treatment of hyperlipidemia, which shall become apparent from the specification which follows, are accomplished by the invention as hereinafter described and claimed.

In general, the present invention provides an improved antihyperlipidemia composition of the oral type employing an effective antihyperlipidemic amount of nicotinic acid, wherein the improvement comprises compounding the nicotinic acid with from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose per hundred parts by weight of table or formulation.

The present invention also provides an orally administered antihyperlipidemia composition which comprises from about 30% to about 90% parts by weight of nicotinic acid; and, from about 5% to about 50% parts by weight of hydroxypropyl methylcellulose.

Generally speaking, the nicotinic acid formulations of the present invention are manufactured by first wet mixing (granulation) niacin and hydroxypropyl methylcellulose, the immediate-release excipient, in a high-energy, high-shear mixer to produce dense niacin pellets. The pellets are then mixed with more hydroxypropyl methylcellulose and compressed into tablets. The resulting tablets are then formed by a mixture of hydroxypropyl methylcellulose-niacin granulation and additional hydroxypropyl methylcellulose.

The present invention also includes a method of treating hyperlipidemia in a hyperlipidemic. The method comprises the steps of forming a composition which comprises an effective antihyperlipidemic amount of nicotinic acid and an amount of excipients to provide intermediate release of drug. The method also includes the step of orally administering the composition to the hyperlipidemic nocturnally.

A method of treating hyperlipidemia in a hyperlipidemic according to the invention, comprises dosing the hyperlipidemic with an effective antihyperlipidemic amount of nicotinic acid or compound metabolized to nicotinic acid by the body. The dose is given once per day in the evening or at night, combined with a pharmaceutically acceptable carrier to produce a significant reduction in total and LDL cholesterol as well as significant reduction in triglycerides and Lp(a), with a significant increase 5 in HDL cholesterol.

Once the niacin formulations of the present invention are swallowed or consumed, the tablets become wet and the hydroxypropyl methylcellulose surrounding the tablets is believed to form thin gel layers. Any granular nicotinic acid exposed to the exteriors of the tablets will dissolve out of the tablets resulting in an intermediate rate of nicotinic acid for absorption. As the nicotinic acid leaves the outer surfaces of the tablets, gastrointestinal fluid can reach deeper into the tablets resulting in thicker gel layers and the dissolution of the intermediate release nicotinic acid granules surrounded by the gel layers. The gel layers then act as controlled release layers for dissolved nicotinic acid originating in the intermediate release nicotinic acid granules.

The above features and advantages of the present invention will be better understood with reference to the following Figs., detailed description and examples. It should also be understood that the particular methods and formulations illustrating the present invention are exemplary only and not to be regarded as limitations of the present invention.

Description of the Figs.

With reference to the accompanying Figs., which are illustrative of certain embodiments within the scope of this invention:

Fig. 1 is a graph depicting the typical *in vitro* dissolution profiles of an immediate release niacin formulation and a sustained release niacin formulation;

Fig. 2 is a schematic depicting the metabolic pathways of niacin in the liver and the niacin metabolites that are common to all niacin formulations, including the immediate and sustained release formulations. Pathway 1 includes niacin and nicotinuric acid (NUA) and Pathway 2 includes the

Phase I metabolites, nicotinamide (“NAM”), 6-hydroxy nicotinamide (“6HN”), nicotinamide-N-oxide (“MNO”), N-methyl-nicotinamide (“MNA”) and nicotinamide adenine dinucleotide (“NAD”). Fig. 2 also depicts that Pathway 2 includes the metabolites of MNA, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY), and the entire NAD cycle which is necessary in nearly all biochemical processes within the cells;

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Fig. 3 is a graph depicting an *in vivo* stair-stepped or sigmoidally-shaped absorption profile or curve which has been deconvoluted using the Wagner-Nelson method from the mean of plasma curves for niacin released from Niaspan® formulations of the instant invention. The profile shows that niacin is absorbed at a lesser rate during about the first two hours and at a significantly faster rate between about hours 2 and 7 following ingestion. The profile also shows that approximately 100% of the absorbable niacin is absorbed at about 7.3 hours after ingestion;

Fig. 4 is a graph depicting individual *in vitro* dissolution profiles of a Niaspan® formulation and thirteen (13) commercially available sustained release niacin formulations; and

Fig. 5 is a chart depicting the percent of a niacin dose recovered in urine as metabolites following consumption of a dose of 500mg of Nicolar®, an immediate release niacin product, doses of 2000mg, 1500mg and 1000mg of Niaspan®, and a dose of 2000mg of Goldline’s time released niacin, a sustained release product. The Phase I pathway concerns those metabolites that are generated by the oxidative pathway. The Phase II pathway includes niacin and nicotinuric acid (NUA) metabolites. The chart shows that a 1500mg dose of Niaspan® produces less Phase II pathway metabolites than a 1500mg dose of an immediate release niacin formulation, i.e., Nicolar®. The chart also shows that a 2000mg dose of Niaspan® produces less Phase I pathway oxidative metabolites than a similar dose of a sustained release niacin product, i.e., Goldline’s timed release niacin.

Detailed Description of the Invention

By way of illustrating and providing a more complete appreciation of the present invention and many of the attendant advantages thereof, the following detailed description and examples are given concerning the novel methods and formulations.

Turning now to the biopharmaceutic characteristics of the novel nicotinic acid formulations, the nicotinic acid formulations of the present invention exhibit an *in vivo* stair-stepped or sigmoidal-shaped profile when the plasma curves for nicotinic acid or NUA are deconvoluted using the Wagner-Nelson method, as taught in Wagner, J.G. *et al.*: *J Pharm Sciences*, 52:610-611 (1963), which is incorporated herein by reference in its entirety. As illustrated in Fig.3, the stair-stepped or sigmoidal-shaped time plot for nicotinic acid absorbed from the formulations of the instant invention is characterized by three phases, designated as phases A, B and C, and by the fact that significant quantities of nicotinic acid are absorbed from such formulations during phases A and B, and predominantly during phase B. Phase A constitutes the initial time period where minimal absorption of nicotinic acid occurs, whereas phase B represents the period time that follows phase A where most of the absorption of nicotinic acid occurs. Phase C concerns that period of time when absorption of nicotinic acid generally ends.

In accordance with the present invention, phase A generally occurs at from about 1 to about 4 hours with a mean of about 2.3 hours after ingestion, and phase B generally occurs for about 4 to about 8 hours with a mean of about 5 hours after phase A. Phase C generally occurs at about 5 to about 9 hours with a mean of about 7.3 hours after ingestion. See Tables 1 and 2. Also reported in Table 1, up to about 19% and preferably about 6.4% is absorbed during phase A, between about 78% and 100% and preferably about 90% is absorbed during phase B, with the remainder, if any, being absorbed during phase C.

As indicated above, deconvolution is calculated using the Wagner-Nelson method of plasma niacin or NUA data generated from frequent blood sampling following the administration of the formulations of the present invention to healthy human volunteers resulting in a percent absorbed time plot which is described in three phases:

Phase A - the initial time period where minimal absorption occurs;

Phase B - the subsequent time period where most of the absorption occurs; and

Phase C - the time when absorption has ended.

The expected values describing each Phase are recited in Table 1:

TABLE 1

	Start (hrs)	Start range (hrs)	% Dose Absorbed/hr	Absorption rate range	End (hrs)	End range (hrs)	% Dose Absorbed	% Dose Absorbed Range (%/hr)
Phase A	0	NA	3.3	0 - 9.2	2.3	1.1 - 4.1	6.4	0 - 1.91
Phase B	2.3	1.1 - 4.1	19.0	14.1 - 26.1	7.3	5.1 - 9.1	90.7	78.4 - 100.4
Phase C	7.3	5.1 - 9.1	0	0	NA	NA	97.1	85.7 - 103.7

Table 2 represents the absorption rate parameters of nicotinic acid in 12 individuals, who each ingested two, 1000mg tablet of Niaspan®, and the minimum, maximum, mean and median for each of those 12 individuals tested. Table 1 is a summary of the results in Table 2.

TABLE 2

Subject	First Absorption		Second Absorption		End Second Absorption Phase (hr)
	Rate (% Dose/Hr)	Absorption Phase (hr)	Rate (% Dose/Hr)	Absorption Phase (hr)	
1	1.90	4.08	21.82	8.08	
2	4.07	2.08	15.86	8.08	
3	5.55	2.08	20.94	6.08	
4	4.39	1.08	15.57	7.08	
5	9.16	2.08	26.12	5.08	
6	4.07	1.08	23.22	5.08	
7	0.00	3.08	14.28	9.08	
8	3.24	2.08	18.08	7.08	
9	0.00	2.08	25.10	6.08	
10	0.00	2.08	16.21	8.08	
11	6.96	2.08	14.09	8.08	
12	0.00	3.08	16.54	9.08	
Mean	3.28	2.25	18.99	7.25	
Minimum	0.00	1.08	14.09	5.08	
Maximum	9.16	4.08	26.12	9.08	
Median	3.65	2.08	17.31	7.58	

The unique nicotinic acid formulations of the present invention therefore result in subsequently all of the nicotinic acid being absorbed within about 5 to about 9 hours, preferably between about 6 and about 8 hours and most preferably between about 7 and 8 hours, following ingestion. Minimal nicotinic acid is absorbed thereafter. It is believed that Phase A results in the plasma concentration of nicotinic acid or NUA prior to the saturation of Pathway 2, whereas phase B concerns the plasma concentration of nicotinic acid or NUA after Pathway 2 has been saturated. It is further believed that the stair-stepped or sigmoidal-shape developed for NUA are as reliable as that developed for nicotinic acid, since the Tmax and shape of the plasma curve parallels the Tmax and shape of the plasma curve for nicotinic acid. The initial absorption of nicotinic acid allows for the initial obtainment of therapeutic levels of nicotinic acid and the second absorption period, phase B, optimizes therapeutic levels thereafter.

Each nicotinic acid formulation of the instant invention will typically exhibit the following dissolution profile in U.S.P. XXIII, Apparatus I, 900mls of deionized water at 37°C., baskets at 100 RPM, as indicated in Table 3.

TABLE 3

Time (hours)	Niaspan® Specification Percent Dissolved	Dissolution range for all Niaspan® strengths tested in humans	Dissolution range for FDA approved Niaspan® tablet batches for all strengths
0	0	0	0
1	less than 15	9.6 - 13.8	9.8 - 12.3
3	15 - 30	21.2 - 27.8	20.9 - 26.7
6	30 - 45	35.1 - 44.2	35.3 - 44.1
9	40 - 60	45.6 - 58.5	44.8 - 58.7
12	50 - 75	56.2 - 72.0	59.5 - 70.7
20	greater than 75	78.1 - 103.9	84.4 - 120.5

By the term "dissolution," it is used herein to refer to that percent of a drug, e.g., nicotinic acid, which is dissolved or released *in vitro* from a formulation into a dissolution medium over a selected period of time under certain conditions. With respect to the shape of the dissolution curve concerning the specifications in Table 3 relative to a target dissolution curve for each Niaspan® tablet strength, the target dissolution curve for each of the Niaspan® tablet strengths are as follows:

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TABLE 4

Time (hours)	250 and 325 mg (% released)	500mg (% released)	750mg (% released)	1000mg (% released)
0	0	0	0	0
1	11.3	10.6	10.3	11.8
3	24.1	22.9	22.0	25.5
6	40.2	38.0	36.60	41.3
9	54.2	51.4	49.4	54.8
12	67.0	63.4	61.6	66.3
20	91.7	88.4	87.2	98.4

It is believed that the nicotinic acid formulations of the present invention are responsible for a controlled absorption profile that is intermediate to that of IR and SR nicotinic acid formulations currently commercially available. As depicted in Fig. 4 and Tables 3, 4, 5A and 5B, and especially 20 Tables 5A and 5B, the dissolution profile of the nicotinic acid formulations of the present invention, i.e., Niaspan®, is slower than that of IR niacin, but different than that of SR niacin commercially available products. The uniqueness of the dissolution profile for the nicotinic acid formulations of the present inventions is shown in Fig. 4 and Tables 3, 4, 5A and 5B.

Tables 5A and 5B depict dissolution data for two representative lots of Niaspan® 500mg 25 tablet strength and other commercially available SR nicotinic acid 500mg products. The dissolution

data of Table 5 represents two lots of Niaspan® 500mg tablets which fall within the range of the dissolution profile provided for Niaspan® tablets of the present invention. Also as illustrated in Fig. 4 and Tables 3, 4 and 5A and 5B, and in particular Tables 5A and 5B, when the dissolution profiles of sixteen (16) over-the-counter SR niacin products are compared to that of Niaspan®, none of the dissolution curves for those products are equivalent to that of Niaspan®.

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TABLES 5A and 5B

Brand Comparison

Table 5A

Time	Niaspan® 500mg	Niaspan® 500mg	Low Limit	High Limit	Goldline 86 86A6014C	Nicobid MN0928	Goldline 12 12L51229	Goldline 87 87L51081	Goldline 89 89G5612C	Rugby MO M070E	Rugby SL 5L01707	Time Cap A051
hrs	500mg	500mg			250mg	500mg	500mg	500mg	500mg	500mg	500mg	
0	0	0	-	-	0	0	0	0	0	0	0	0
1	10.3	10.8		15	5.4	4.9	12.6	10.8	16.5	16.7	11.7	14.9
3	22.5	23.9	15	30	16.9	14.4	28.0	26.5	39.0	40.6	27.1	32.4
6	37.6	39.0	30	45	32.9	26.9	47.8	43.9	57.3	62.9	46.1	50.6
9	51.2	51.8	45	60	42.9	37.0	58.8	58.0	67.3	73.0	60.4	62.9
12	62.8	63.1	50	75	56.0	43.9	65.7	69.4	73.0	81.7	72.2	70.3
20	87.1	85.2	75		72.8	58.3	77.0	91.7	81.6	89.3	94.3	81.3

Table 5B

Time	Niaspan® 500mg	Niaspan® 500mg	Low Limit	High Limit	Major 5F00753	Upsher-S 16020	Geneva 4B124	Mason 501199	Endurance 11504	Rugby K053G	Nicobid MN1937	Goldline 89A51566
hrs	500mg	500mg			500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg
0	0	0	-	-	0	0	0	0	0	0	0	0
1	10.3	10.8		15	16.6	13.7	20.7	11.3	11.0	31.9	10.8	11.0
3	22.5	23.9	15	30	38.7	28.1	43.2	27.1	24.2	42.2	27.2	30.6
6	37.6	39.0	30	45	53.7	45.7	60.0	45.4	36.5	61.0	38.1	53.2
9	51.2	51.8	45	60	61.7	61.4	71.5	60.4	48.1	72.9	51.5	
12	62.8	63.1	50	75	70.6	73.5	77.8	71.0	56.4	77.9	61.1	74.7
20	87.1	85.2	75		78.3	92.8	87.6	90.5	71.9	84.0	75.9	85.6

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Similarity between the test and the target dissolution curves within a tablet strength can be determined through the calculation of the fit factor F_2 . See Moore JW, Flanner HH.: Mathematical comparison of dissolution profiles, Pharmaceutical Technology, 64-74 (June 1996), which is incorporated herein by reference in its entirety. In other words, the fit factor F_2 is calculated using the difference between the percent dissolved at each time point for each dissolution profile. If there
5 is no difference between the percent dissolved at each time point, the fit factor F_2 equals 100. As the difference in percent dissolved increases, however, the fit factor F_2 value decreases. The fit factor F_2 is determined by the following equation:

$$F_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t is the dissolution value for the target profile at a time point t , T_t is the dissolution value for the test profile at the same time point t , n is the number of time points on the dissolution profile and w_t is an optional weight factor. This equation is a logarithmic transformation of the sum of the mean square error between the test and target profile, resulting in a number between 0 and 100. The fit factor F_2 is 100 when two dissolution profiles are identical and decreases as the two profiles become more dissimilar. In other words, the smaller the fit factor F_2 , the farther apart the products are from
20 one another. The fit factor F_2 will be positive as long as the average difference between the two curves is 100 or less.

The following Table 6 depicts the recommended fit factor F_2 values for each of the Niaspan® tablet strengths. The recommended values are based on the range of fit factors F_2 between lots used in the New Drug Application (NDA), made more specific by the determination of bioequivalence to
25 a target lot of Niaspan® tablets.

TABLE 6

Criteria derived from:	250 and 325 mg tablet strengths	500mg tablet strength	750mg tablet strength	1000mg tablet strength
Bioequivalence Studies	≥79.0	≥79.0	≥79.0	≥44.0

The term "bioequivalence," as used herein, means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See Code of Federal Regulations, Title 21, April 1, 1997 edition, Part 320.1, Definitions (e) *Bioequivalence*, page 195, which is incorporated by reference herein in its entirety.

Table 7 also depicts the fit factor F_2 for thirteen (13) of the sixteen (16) over-the-counter SR niacin products referenced in Tables 5A and 5B compared to the dissolution curve of Niaspan®. As can be seen from the fit factor F_2 data in Table 7, the thirteen (13) over-the-counter SR niacin products are not bioequivalent to Niaspan®, in view of the fact that the fit factor F_2 is less than 79 for all such products.

TABLE 7

Brand	Niaspan®	GTRN 250	Nicobid	Goldline 12	Goldline 87	Goldline 89	Rugby M0	Rugby SL	Time Cap	Major	Upsher-Smith	Geneva	Mason	Endurance
K4061A-1	86A6014C	MN0928	12L51229	87L51081	89G5612C	M070E	SL01707	A051G	5F00753	16020	4B124	501199	11504	
	500mg	250mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg
F2	79	54.3	39.4	60.6		64.5	45.0	38.7	57.3	53.9	48.7	56.3	39.3	60.8
	59.6													

The percent of the dose excreted in urine as niacin and NUA as well as the percent of the dose excreted in urine as metabolites other than niacin and NUA relative to the total dose recovered is due to saturable first-pass metabolism. Thus, because it is now discovered that the rate of niacin absorption determines the amount of drug that is excreted as niacin and NUA versus all other niacin metabolites, the rate of absorption can be used to control the amount of Pathway 1 and Pathway 2 metabolites produced. This can be depicted from urine collection data obtained following multiple-daily administrations of Niaspan® to healthy human volunteers, as illustrated in Table 8.

TABLE 8

Metabolites recovered	2x500mg Niaspan® tablets	2x750mg Niaspan® tablets	2x1000mg Niaspan® tablets	3x1000mg Niaspan® tablets
Niacin + NUA				
Mean	12.2%	21.3%	32.4%	41.9%
Range	4.5 - 25.7%	11.0 - 44.8%	21.7 - 48.2%	25.4 - 66.1%
All others				
Mean	87.8%	78.7%	67.6%	58.1%
Range	74.3 - 95.5%	55.2 - 89.0%	51.8 - 78.3%	33.9 - 74.6%

Table 8 reflects the range and mean of metabolites recovered in the urine from 27 individuals at 24 hours after administration of the respective Niaspan® tablet strengths once per day at night for 6 days. The numbers recited in Table 8 represent the mean and range for all 27 patients for each dosage regimen.

Turning now to Fig. 5, it depicts actual metabolite recovery data from two studies involving six subjects where the amount of Phase I pathway (Pathway 2) and Phase II pathway (Pathway 1) metabolites excreted in urine at steady-state following the administration of IR (500mg tid) and SR niacin (500mg qid), which were quantified. Fig. 5 further depicts that SR niacin results in little Phase II pathway (Pathway 1) metabolites (niacin and nicotinuric acid) and that almost all of the niacin from the SR formulation was converted to Phase I pathway (Pathway 2) oxidative metabolites.

Moreover, little to no flush was reported by the individuals who received the SR niacin product in this study, while nearly all subjects who received IR niacin experienced flush. Because all six subjects in this study who consumed the SR niacin product experienced elevations in liver enzymes at least 3 times greater than the upper limit of normal, the study was prematurely terminated. In the IR niacin study where much less Pathway 2 metabolites were produced, no subjects experienced elevations in liver enzymes. It is believed that, because the SR niacin products are designed with a slow dissolution or absorption rate which results in a situation where the rate of niacin presentation to the liver is so slow that Pathway 2 is never saturated and the major metabolites produced are Pathway 2 metabolites, hepatotoxicity will ensue from SR niacin products. On the other hand, when IR niacin is administered, it is believed that, because the presentation of niacin to the liver is so rapid that Pathway 2 is saturated almost immediately, the major metabolites produced are Pathway 1 metabolites and the patient experiences flush.

As compared to the IR and SR niacin formulations, the unique absorption rate of Niaspan® is believed to result in a urine metabolite profile that balances the extremes of these two metabolic profiles. In other words, the unique absorption profile following Niaspan® administration balances the Pathway 1 and Pathway 2 metabolites thereby minimizing the risk of drug-induced hepatotoxicity at the expense of possibly causing some flush. To minimize the flush, the unique titration regimen recommended at the beginning of Niaspan® therapy is designed to allow the body to down regulate or desensitize itself from the prostaglandin effects (PGD₂) resulting from the administration of niacin. For those individuals who are initiating niacin therapy, it is possible to avoid significant flushing by starting with a unique Niaspan® titration pack. In accordance with the present invention, the novel titration packs include Niaspan® tablets in at least the following three dosage regimens, i.e., 375mg, 500mg and 750mg, and are generally administered as follows: the new patient receives Niaspan® 375mg Once-A-Night™ for seven days, followed by Niaspan® 500mg Once-A-Night™ for seven days, and then Niaspan® 750mg Once-A-Night™ for seven days, after which they may start receiving therapeutic doses of Niaspan® starting at 1000mg Once-A-Night™ as two, 500mg tablets.

Once titrated, it is important for the patients to take therapeutic doses of Niaspan® as directed in the labeling to avoid the risk of significant flushing early in the initial therapy and hepatotoxicity later in the therapy. That is, patients should take two, 500mg Niaspan® tablets for a 1000mg dose, two, 750mg Niaspan® tablets for a 1500mg dose and two, 1000mg Niaspan® tablets for a 2000mg dose. It is believed that early flushing and subsequent hepatotoxicity can be avoided by following such 5 directions in view of the fact that the 350mg and 500 mg Niaspan® tablets are not bioequivalent to the 750mg and 1000mg tablets, i.e., the 375mg, 500mg and 750mg Niaspan® tablets release niacin at a slower rate than the Niaspan® 1000mg tablets. Moreover, the 375mg and 500mg Niaspan® tablets are believed to release niacin at the slowest rate. Thus, and in accordance with the present invention, early in niacin therapy, when a patient is most susceptible to flush and taking low doses, the patient should receive the slower dissolving Niaspan® tablets to avoid quick saturation of Pathway 2 and to permit the body to desensitize itself from the prostaglandin effects (PDG₂) resulting from elevated niacin concentrations, so that flush can be avoided. However, as the patient is titrated to higher doses (no more than about 500mg increments at four-week intervals), the Niaspan® tablets used should release their niacin at faster rates to reduce the risk of hepatotoxicity. It is believed that, at this point, the patients prostaglandin system has acclimated itself to niacin and the risk of flush is minimized.

Other biopharmaceutic characteristics of the Niaspan® tablets include AUC, Cmax and Tmax. By the term "AUC," it refers to the area under a plasma concentration curve of niacin or NUA and is based upon the rate and extent of absorption of niacin following ingestion of a certain dose of a niacin formulation. By the term "Cmax," as used herein, it is meant to refer to the peak or maximum concentration of niacin or NUA achieved in the plasma following ingestion of a certain dose of a niacin formulation. Cmax occurs generally at about the time when the niacin in the formulation has been almost completely absorbed therefrom, and it too is based upon the rate and extent of absorption of niacin following ingestion of a certain dose of a niacin formulation. The term 20 "Tmax" refers to the time that Cmax occurs following ingestion. The Tmax for the Niaspan® 25

products of the present invention generally occurs between about 5.6 hours and about 6 hours following ingestion, which believed to be due in part to the saturable first pass effect of the liver.

Turning now to Table 9, it depicts both AUC and Cmax data for niacin and NUA obtained from the administration of a single dose of Niaspan® at the dosage strengths identified therein to individuals from whom blood was withdrawn at frequent intervals over a 24 hour period following 5 ingestion to detect the niacin and NUA concentrations from which the absorption rate of niacin can be determined. According to Table 9, the 375mg Niaspan® tablets have a niacin Cmax of about 3.39 $\mu\text{g}/\text{ml}$ and AUC of about 5.8 $\mu\text{g}\text{hr}/\text{ml}$ and an NUA Cmax of about 2.4 $\mu\text{g}/\text{ml}$ and an AUC of about 9.6 $\mu\text{g}\text{hr}/\text{ml}$. Table 9 further reports that the 500mg Niaspan® tablets have a niacin Cmax in the range of from about 1.13 $\mu\text{g}/\text{ml}$ to about 10.1 $\mu\text{g}/\text{ml}$ with a mean of about 3.71 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 1.8 $\mu\text{g}\text{hr}/\text{ml}$ to about 33.7 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 8.9 $\mu\text{g}\text{hr}/\text{ml}$. Still further, Table 9 reports that the 500mg Niaspan® tablets have an NUA Cmax in the range of about 1.62 $\mu\text{g}/\text{ml}$ to about 3.4 $\mu\text{g}/\text{ml}$ with a mean of about 2.18 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 5.5 $\mu\text{g}\text{hr}/\text{ml}$ to about 15.7 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 8.7 $\mu\text{g}\text{hr}/\text{ml}$.

Table 9 further reports that the 750mg Niaspan® tablets have a niacin Cmax in the range of from about 7.68 $\mu\text{g}/\text{ml}$ to about 9.11 $\mu\text{g}/\text{ml}$ with a mean of about 8.40 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 21.1 $\mu\text{g}\text{hr}/\text{ml}$ to about 21.5 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 21.3 $\mu\text{g}\text{hr}/\text{ml}$. Still further, Table 9 reports that the 750mg Niaspan® tablets have an NUA Cmax in the range of about 2.97 $\mu\text{g}/\text{ml}$ to about 3.2 $\mu\text{g}/\text{ml}$ with a mean of about 3.09 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 11.5 $\mu\text{g}\text{hr}/\text{ml}$ to about 12.7 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 12.1 $\mu\text{g}\text{hr}/\text{ml}$.

Table 9 further reports that the 1000mg Niaspan® tablets have a niacin Cmax in the range of from about 9.29 $\mu\text{g}/\text{ml}$ to about 16.6 $\mu\text{g}/\text{ml}$ with a mean of about 12.54 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 24.2 $\mu\text{g}\text{hr}/\text{ml}$ to about 42.6 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 33.2 $\mu\text{g}\text{hr}/\text{ml}$. Still further, Table 9 reports that the 1000mg Niaspan® tablets have an NUA Cmax in the range of about 2.81 $\mu\text{g}/\text{ml}$ to about 4.45 $\mu\text{g}/\text{ml}$ with a mean of about 3.55 $\mu\text{g}/\text{ml}$ and an AUC in the range of about 12.0 $\mu\text{g}\text{hr}/\text{ml}$ to about 18.8 $\mu\text{g}\text{hr}/\text{ml}$ with a mean of about 15.4 $\mu\text{g}\text{hr}/\text{ml}$.

TABLE 9

Dose mg	Study	Tablet mg	Niacin		NUA	
			Cmax ug/ml	AUC ughr/mL	Cmax ug/ml	AUC ughr/mL
	1500 A	375	3.39	5.8	2.4	9.6
	1500 B	500	10.1	33.7	3.4	15.7
5	1500 C	500	5.76	15.7	2.33	10.1
	1500 C	500	5.98	15.8	2.33	10.2
	1500 A	500	3.04	5.8	2.25	9
	1500 D	500	2.89	4.76	2.16	7.6
10	1500 D	500	3.14	5.1	2.31	8.6
	1500 D	500	2.36	3.1	1.98	7.2
	1500 E	500	1.81	3.1	1.89	7
	1500 E	500	1.13	1.8	1.62	5.5
15	1500 E	500	1.69	2.2	1.8	6
	2000 F	500	4.66	11.6	2.28	9.3
	2000 G	500	2.02	4.6	2.06	9.0
	1500 H	750	9.11	21.5	3.2	11.5
	1500 I	750	7.68	21.1	3.2	11.5
	2000 G	1000	11.6	31.4	3.35	14.3
20	2000 G	1000	9.39	24.2	2.91	12
	2000 J	1000	15.8	42.6	4.21	18.4
	2000 J	1000	16.6	41.4	4.45	18.8
	2000 K	1000	9.29	26.2	2.81	13.3

Turning now to the Once-A-Night™ administration of Niaspan®, it is believed that a significant amount of lipid synthesis occurs at night. Thus, it is believed that the administration of Niaspan® in the evening or at bedtime produces niacin concentrations in the body at the optimal time necessary to interfere with the conversion of free fatty acids into LDL-cholesterol, thereby producing its beneficial effects. The Once-A-Night™ administration regimen is also believed to minimize the risk of hepatotoxicity as follows. Because SR niacin is generally administered at least twice daily and Niaspan® is administered once-daily at night, the SR niacin products will result in a greater accumulation of Pathway 2 metabolites because it is re-administered before sufficient metabolite has left the body. As a consequence, the Pathway 2 metabolites will pass over the toxic threshold causing drug-induced hepatotoxicity. On the other hand, Niaspan® produces less Pathway 2 metabolite and is administered less frequently allowing sufficient time for clearance of metabolites keeping their accumulation below the toxic threshold. Thus, it is believed that the unique combination of the controlled niacin absorption rate of Niaspan®, the adherence to the Niaspan® titration schedule and/or the Once-A-Night™ administration regimen are responsible for the efficacy of Niaspan® and the minimized flush and hepatotoxicity associated with its administration. In other words, it is believed that Niaspan's® unique absorption rate profile combined with its unique titration schedule and its unique Once-A-Night™ regimen are responsible for its lower incidence of flush relative to IR niacin, its minimal risk of drug-induced hepatotoxicity relative to SR niacin, and its efficacy in hyperlipidemia.

The present invention employs nicotinic acid or a compound other than nicotinic acid itself which the body metabolizes into nicotinic acid, thus producing the same effect as described herein. The other compounds specifically include, but are not limited to the following: nicotinyl alcohol tartrate, d-glucitol hexanicotinate, aluminum nicotinate, nericinol and d,1-alpha-tocopheryl nicotinate. Each such compound will be collectively referred to hereinbelow by "nicotinic acid."

As stated hereinabove, nicotinic acid has been employed in the past for the treatment of hyperlipidemia, which condition is characterized by the presence of excess fats such as cholesterol and triglycerides, in the blood stream. According to the present invention, an intermediate release

composition of nicotinic acid is prepared as an example. As indicated herein, "intermediate release" is understood to mean a composition or formulation which, when orally administered to a patient to be treated, the active ingredient will be released for absorption into the blood stream over a period of time which is slower than that of IR niacin formulations, but faster and different than SR niacin products. For example, it is preferred that in a dosage of about 1000-3000 milligrams (herein "mg(s)") of nicotinic acid, approximately 100 percent of the nicotinic acid will be released to the blood stream in about 5 to about 9 hours.

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The specific intermediate release composition according to the present invention employs an effective antihyperlipidemic amount of nicotinic acid. By "effective antihyperlipidemic amount" it is understood to mean an amount which when orally administered to a patient to be treated, will have a beneficial effect upon the physiology of the patient, to include at least some lowering of total cholesterol, LDL cholesterol, triglycerides and Lp(a) and at least some increase in HDL cholesterol in the patient's blood stream. An exemplary effective antihyperlipidemic amount of nicotinic acid would be from about 250 mgs to about 3000 mgs of nicotinic acid to be administered according to the invention as will be more fully described hereinbelow. This amount will very dependent upon a number of variables, including the psychological needs of the patient to be treated.

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Preferably, there is also included in the intermediate release composition according to the present invention, a swelling agent which is compounded with the nicotinic acid, such that when the composition is orally administered to the patient, the swelling agent will swell over time in the patient's gastrointestinal tract, and release the active nicotinic acid, or a compound which produces nicotinic acid into the gastrointestinal system for absorption into the blood stream, over a period of time. As is known in the art, such swelling agents and amounts thereof, may be preselected in order to control the time release of the active ingredient. Such swelling agents include, but are not limited to, polymers such as sodium carboxymethylcellulose and methylcellulose and waxes such as bees wax and natural materials such as gums or gelatins or mixtures of any of the above. Because the amount of the swelling agent will vary depending upon the nature of the agent, the time release needs of the

patient and the like, it is preferred to employ amounts of the agent which will accomplish the objects of the invention.

An exemplary and preferred swelling agent is hydroxypropyl methylcellulose, in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of tablet or formulation. The preferred example will ensure a sustained time release over a period of approximately 5-9 hours as demonstrated by in vitro dissolution techniques known to the art.

A binder may also be employed in the present compositions. While any known binding material is useful in the present invention, it is preferred to employ a material such as one or more of a group of polymers having the repeating unit of 1-ethenyl-2-pyrrolidinone. These polymers generally have molecular weights of between about 10,000 and 700,000, and are also known as "povidone".

Amounts of the binder material will of course, vary depending upon the nature of the binder and the amount of other ingredients of the compositions. An exemplary amount of povidone in the present compositions would be from about 1% to about 5% by weight of povidone per 100 parts by weight of the total formulation.

Processing aids such as lubricants, including stearic acid, may also be employed, as is known in the art. An exemplary amount of stearic acid in the present compositions would be from about 0.5% to about 2.0% by weight per 100 parts by weight of table or formulation.

Examples of various embodiments of the present invention will now be further illustrated with reference to the following examples.

20

General Experimental

In order to demonstrate the effectiveness of the compositions and method of the present invention over known antihyperlipidemia compositions and methods heretofore known in the art, a number of substantially identical composition were prepared according to the disclosure hereinabove. The composition ingredients and amounts are listed in Table IA hereinbelow.

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TABLE IA
Test Tablet Composition

<u>Ingredient</u>	<u>375 mg</u>	<u>500 mg</u>	<u>750 mg</u>
Nicotinic Acid	375.0	500.0	750.0
Hydroxypropyl methylcellulose	188.7	203.0	204.7
Povidone	12.9	17.2	25.9
Stearic Acid	5.8	7.3	9.9
TOTAL	582.4 mg	727.5 mg	990.5 mg

The ingredients were compounded together to form a tablet. More specifically, Niaspan® once-daily tablets in accordance with the present invention utilize a hydrophilic matrix controlled drug delivery system. This is a dynamic system composed of polymer wetting, polymer hydration and polymer disintegration/dissolution. The mechanism by which drug release is controlled depends on, for example, initial polymer wetting, expansion of the gel layer, tablet erosion and niacin solubility. After initial wetting, the hydrophilic polymer starts to partially hydrate, forming a gel layer. As water permeates into the tablet increasing thickness of the gel layer, drug diffuses out of the gel layer. As the outer layer of the tablet becomes fully hydrated it erodes. It is believed that this erosion results in additional drug release. The controlled release from this matrix delivery system can be modified depending on the type of molecular weight of hydrophilic polymer used.

A Niaspan® formulation consists of Niacin, Methocel® E10M Premium, Povidone K90 and Hystrene 5016 (stearic acid). Methocel® E10M Premium is utilized as a controlled-release agent in the Niaspan® formulation. Methocel is a partly O-methylated and O-(2-hydroxypropylated) cellulose and is available in several grades which vary in terms of viscosity and degree of substitution.

Methocel is manufactured by Dow Chemical.

Povidone K90 is employed as a granulating/binding agent in a Niaspan® formulation. Povidone is a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidone groups, the degree of

polymerization of which results in polymers of various molecular weights, or as indicated above. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. Povidone K90 has an approximate molecular weight of 1,000,000. Povidone is a hygroscopic, water soluble material. Povidone K90 presents in a Niaspan® formulation is manufactured by ISP (International Speciality Products). Hystrene 5016 is utilized as an external lubricant in the Niaspan® formulation. Hystrene 5016 is a mixture of stearic acid and palmitic acid. The content of stearic acid is not less than about 40.0% and the sum of the two acids is not less than about 90.0%. Hystrene 5016 is manufactured by Witco. Refer to Table IB for Niaspan® formulation details.

Qualitatively, the four tablet strength formulations are identical. The major component of each formulation is a granulated mixture of Niacin, Methocel E10M and Povidone K90. The granulation process improves compression properties.

TABLE IB
Niaspan® Tablet Formulations

Niaspan® Product	375mg Tablets	500mg Tablets	750mg Tablets	1000mg Tablets
<u>Formulation, % Tablet</u>				
Niacin	64.4	70.5	77.4	83.1
Methocel E10M	7.4	8.1	8.9	9.5
Premium (Intrgranular)				
Povidone K90	2.2	2.4	2.7	2.9
Methocel E10M				
Premium (Extrgranular)	25.0	18.0	10.0	3.5
Hystrene 5016 (Stearic Acid)	1.0	1.0	1.0	1.0
Tablet weight, mg	582.5	709.5	968.6	1203.6

Niaspan® formulations are presented in white caplet shape tablets. Caplet dimensions differ with respect to product strength. The 375mg and 500mg Niaspan® tablets are compressed with tooling measuring approximately 0.687" in length x 0.281" by width. The length and width of the 750mg and 1000mg tooling measures approximately 0.750" x 0.320". Target tablet weight and

hardness dictate thickness across the four Niaspan® products. The production of the Niaspan® tablets will now be described generally as set forth below.

Niaspan® Granulation Process Flow Chart

	<u>Raw Materials</u>	<u>Process Flow</u>	<u>Equipment</u>
5	Niacin	Granulate	High shear granulator (Littleford FM130)
	Povidone K90		
	Methocel E10M (Intragrangular)		
10	Purified Water		
		Dry	Fluid bed drier (Gladd fluid bed drier)
		Parcel size reduction	Mill (Kemutec Betagrind)

Niaspan® Granulation Process Description

Niaspan® granulation raw materials are dispensed and granulated in a high shear granulator. The wet granules are sieved into a fluid bed drier and dried. When the drying process is complete, the granules are milled. Milling ensures uniform particle size distribution throughout the Niaspan® granulation.

Niaspan® Tablet Process Flow Chart

	<u>Raw Materials</u>	<u>Process Flow</u>	<u>Equipment</u>
25	Methocel E10M (Extragrangular)	Niaspan® Tablet Blend Blend Milled Niaspan® granules with extragrangular Methocel E10M and Hystrene 5016	Blender (Patterson-Kelley V-Blender)
30	Hystrene 5016 (Stearic acid)		
		↓ Niaspan® Table Manufacture Compress Niaspan® Tablet Blend	Rotary tablet press

Niaspan® Tablet Process Description

A Niaspan® tablet blend is manufactured by blending the Niaspan® granulation, extragranular Methocel E10M and Hystrene 5016. The quantities of each Niaspan® tablet blend component will depend on the particular Niaspan® dose being manufactured (refer to Table IB). A Niaspan® tablet blend is compressed to form Niaspan® tablets. Niaspan® tablet physical properties will vary depending on the particular Niaspan® dose being manufactured.

5 Production of Niaspan® tablets will now be discussed in greater detail. The initial stage of manufacturing is the same for all four tablet strengths of Niaspan® (375, 500, 750 and 1000mg). One batch of Niaspan® granulation is comprised of four individual 40.0kg unites of granulation which are processed separately, but under like conditions. The four individual granulations are sampled and tested individually and subsequently released for blending. The base granulation is not strength specific and may be used to manufacture any tablet strength of Niaspan®.

10 The ingredients in the base granulation are set forth in Table IC below:

15 **TABLE IC**

Component	Function	Quantity per kilogram granulation (kg)	% per kilogram granulation (%)	Quantity per 160.00 kg batch (kg)
Niacin, USP	Drug Substance	0.87	87.00	139.20
Povidine, UPS	Binder	0.03	3.00	4.80
Methocel USP, E10M Premium CR Grade	Controlled-Release Agent	0.10	10.00	16.00
Purified Water, USP*	Granulation Reagent	0.00*	0.00*	48.0
Total				160.00

20 *Purified Water, USP is used as granulation reagent and does not appear in the finished

25 granulation.

Raw materials are quantitatively dispensed into appropriately labeled double polyethylene-lined containers using calibrated scales. Purified Water, USP is dispensed into an appropriate vessel from which it is later pumped during the wet-massing operation.

A Littleford FM130 granulator is charged with approximately one half of the Niacin, USP required for the process unit (~17.4 kg) followed by about 4.00kg of Methocel, USP E10M Premium CR Grade; about 1.20kg of Povidine, USP; and the balance of the Niacin, SP (~17.40kg). The powder bed is dry mixed in the Littleford FM130 granulator, with choppers on, for approximately 1 minute. At the completion of the 1-minute pre-mix cycle, about 12.0 ± 0.05 kg of Purified Water, USP are sprayed onto the powder bed at a rate of about 2.40 ± 0.24 kg/minute. Immediately following the addition of the Purified Water, USP, the unit is granulated for about 5 minutes.

The granulated unit is discharged into double polyethylene-lined containers and then manually loaded into a Glatt bowl while being passed through a #4 mesh screen. The Glatt bowl is loaded into a Glatt TFO-60 fluid-bed drier with an inlet air temperature setting of about $70^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The unit is dried until a moisture level of $\leq 1.0\%$ is obtained as determined using a Computrac® Moisture Analyzer, model MA5A. The dried granulation is discharged into appropriately labeled, double polyethylene-lined drums and reconciled.

The dried and reconciled granulation is passed through a Kemutec BetaGrind mill equipped with a 1.5mm screen and running at approximately 1500 RPM. The milled granulation is collected into appropriately labeled, double polyethylene-lined drums and reconciled. The milled granulation is sampled and tested by Quality Control and released prior to further processing.

The released granulation units are charged to a Patterson-Kelley 20 ft³ V-blender after which they are blended together for about 10 ± 1 minutes and then discharged to appropriately labeled, double polyethylene-lined containers.

As stated above, Niaspan® tablets are formulated from a common granulation which is blended with appropriate quantities of Methocel, USP E10M Premium CR Grade and Stearic Acid, NF to achieve the final dosage formulation. Tables IA and IB describe the formulation for each Niaspan® tablet strength, 375 mg, 500mg, 750mg and 1000mg, respectively.

Two study groups consisting of eleven and fourteen patients each were formed. Blood samples were taken from the patients, and tested for total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol to establish baseline levels from which fluctuations in these lipids could be compared. The patients were then placed upon a regimen of the above discussed tablets, totaling approximately 1500 mg of nicotinic acid, once per day before going to bed. After eight weeks of this regimen, the patients were again tested for lipid profiles. The results of tests conducted at eight weeks, showing the changes in the lipid profiles as a percentage change from the baseline, are reported in the table hereinbelow. Positive numbers reflect percentage increases and negative numbers reflect percentage decreases in this table.

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TABLE II
Patient Study Lipid Profile Data

<u>Pt. No.</u>	<u>Total-C</u>	<u>LDL-C</u>	<u>Apo B</u>	<u>Trigs</u>	<u>HDL-C</u>	<u>HDL-C</u>	<u>Lp(a)</u>
GROUP A							
1	-8.2	-12.0	NA	-17.3	22.0	NA	NA
2	-5.9	-27.0	NA	-28.7	65.0	NA	NA
3	-15.1	-13.0	NA	-22.0	-9.1	NA	NA
4	-3.3	-10.0	NA	61.6	3.8	NA	NA
5	-16.5	-17.7	NA	-28.8	11.1	NA	NA
6	-12.	-25.9	NA	-42.0	51.6	NA	NA
7	-24.2	-31.4	NA	-30.4	12.5	NA	NA
8	-6.7	-7.4	NA	-42.4	18.8	NA	NA
9	4.5	1.1	NA	7.2	9.2	NA	NA
10	2.8	-0.2	NA	-2.7	22.9	NA	NA
11	-13.0	-9.4	NA	-54.0	44.3	NA	NA
Mean	-8.9	-9.4	NA	-18.9	23.0	NA	NA
p-Value	0.0004-8.9	0.0001-13.9		0.0371	0.0068		

GROUP B

1	-19.2	-27.1	-24.4	-33.4	20.0	22.3	-81.9	
2	-32.2	-35.7	-28.0	-60.4	4.3	3.2	-25.3	
3	-21.4	-33.6	-35.6	-33.4	30.4	38.6	-17.4	
4	-19.9	-24.6	-15.1	-20.8	9.6	16.1	-27.0	
5	5	-3.3	-2.1	-29.4	-41.1	5.8	2.4	-22.4
6	PATIENT WITHDREW FROM STUDY							
7	23.1	-32.6	-42.6	-58.6	49.2	68.9	-14.3	
8	24.8	34.0	-28.4	5.5	6.5	-6.8	Na	
9	10.1	12.0	-16.8	-11.6	2.7	-12.3	40.6	
10	-2.9	-7.7	-28.0	-59.0	53.1	70.5	-41.2	
11	-10.5	-18.8	-25.3	-53.4	31.8	39.7	NA	
12	-20.0	-30.8	-30.4	11.7	21.1	25.0	-28.4	
13	17.4	16.8	-17.5	-17.5	51.3	51.9	38.5	
14	-9.4	-16.6	-32.0	-46.9	52.3	67.6	17.6	
15	MEAN	-8.7	-12.8	-32.2	-27.2	25.3	30.1	-17.9
	p-Value	0.0002	<0.0001	0.0001	<0.001	<0.0001	0.0002	<0.0199
	Combined	-8.7	-13.3	Gp B	-26.1	25.3	Gp B	Gp B
	p-Value	0.0002	<0.0001	only	<.0001	<0.0001	only	only

20 The data reported in Table II shows that the LDL levels in the Group A patients had a mean decrease of -13.9% and triglyceride decrease of -18.9% HDL cholesterol levels, the beneficial cholesterol, were raised by 23.0% in this Group. Similar results were obtained with the Group B patients. These studies demonstrate that dosing the sustained release formulation during the evening hours or at night provides reductions in LDL cholesterol levels equal to immediate release niacin on 25 a milligram per milligram basis, but superior reductions in triglyceride reduction when compared to

sustained release formulations dosed during daytime hours on a milligram per milligram basis. Additionally, the increases in HDL cholesterol obtained from doing the sustained release formulation during the evening or at night were $\pm 23.0\%$ for one group and $+25.3\%$ for the other group. Dosing during the evening therefore provides reduction in LDL cholesterol plus significant decreases in triglycerides and increases in HDL cholesterol with once-a-day dosing.

5 Groups A and B were also tested for liver enzymes (AST, ALT and Alkaline Phosphatase), uric acid and fasting glucose levels at the start of the study described hereinabove (to form a baseline) and at two, four and eight week intervals. The results of these tests are listed in TABLES III-VII hereinbelow.

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TABLE III
THE EFFECT OF NIASPAN® THERAPY ON AST (SGOT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

<u>Pt#</u>	<u>Baseline</u>	<u>2 Wks.</u>	<u>4 Wks.</u>	<u>8 Wks.</u>	<u>Reference Range</u>
GROUP A					
1	28	29	25	24	0-50
2	24	25	24	26	0-50
3	17	18	22	21	0-50
4	14	16	15	17	0-50
5	22	NA	32	52	0-50
6	21	17	17	14	0-50
7	17	17	14	18	0-50
8	20	21	22	22	0-50
9	16	16	17	20	0-50
10	18	21	21	25	0-50

TABLE III (Continued)

11	21	21	22	21	0-50
GROUP B					
1	23	25	38	33	0-50
2	20	20	21	21	050
3	15	20	18	19	0-50
5	4	28	22	28	0-52
	5	23	21	17	0-50
6	PATIENT WITHDREW DUE TO FLUSHING				
7	21	18	18	19	0-50
8	18	19	18	19	0-50
9	15	16	18	15	0-50
10	16	15	19	28	0-50
11	20	22	24	28	0-50
12	23	25	28	22	0-50
13	20	15	20	19	0-50
14	18	25	20	18	0-50
	Combined Mean	19.8	20.4	20.8	21.1
	Change From Baseline		+3.0%	+5.1%	+6.6%

Level of Significance: p=0.4141

TABLE IV
THE EFFECT OF NIASPAN® THERAPY ON ALT (SGPT) LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

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Weeks of Therapy With Niaspan®

<u>Pt#</u>	<u>Baseline</u>	<u>2 Wks.</u>	<u>4 Wks.</u>	<u>8 Wks.</u>	<u>Reference Range</u>
10	GROUP A				
1	32	28	39	30	0-55
2	24	25	23	26	0-55
3	18	23	30	30	0-55
4	7	13	14	14	0-55
15	5	14	NA	43	0-55
6	22	11	14	10	0-55
7	9	7	11	7	0-55
8	16	18	23	21	0-55
9	14	17	20	14	0-55
20	10	14	15	17	0-55
11	18	18	20	16	0-55
25	GROUP B				
1	16	17	27	29	0-55
2	16	14	15	22	0-55
3	13	21	13	16	0-55
4	23	20	26	17	0-55
5	21	23	17	15	0-55
30	6	PATIENT WITHDREW DUE TO FLUSHING			
7	21	16	18	21	0-55
8	18	20	17	18	0-55

TABLE IV (continued)

9	11	5	11	8	0-55
10	8	10	14	17	0-55
11	17	12	18	16	0-55
12	14	18	20	16	0-55
13	14	NA	11	10	0-55
5	14	23	19	19	0-55
	Combined Mean	17.7	17.5	19.3	18.2
	Change From Baseline		-1.1%	9.0%	+2.8%

Level of Significance: p=0.3424

TABLE V
THE EFFECT OF NIASPAN® THERAPY
ON ALKALINE PHOSPHATASE LEVELS (U/L)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

	<u>Pt#</u>	<u>Baseline</u>	<u>2 Wks</u>	<u>4 Wks</u>	<u>8 Wks</u>	<u>Reference Range</u>
GROUP A						
	1	52	56	57	55	20-140
	2	103	100	89	102	20-140
25	3	54	45	53	51	20-140
	4	70	68	71	91	20-140
	5	77	NA	74	81	20-140
	6	55	48	49	51	20-140
	7	72	71	79	75	20-140
30	8	55	49	47	50	20-140

TABLE V (Continued)

9	53	55	56	45	20-140
10	74	73	75	75	20-140
11	18	18	20	16	20-140
GROUP B					
1	73	67	89	95	20-140
5	2	82	64	72	20-140
3	73	69	81	82	20-140
4	37	36	37	38	20-140
5	65	53	54	61	20-140
6	PATIENT WITHDREW DUE TO FLUSHING				
7	64	58	58	58	20-140
8	79	78	65	73	20-140
9	94	92	103	93	20-140
10	69	67	70	65	20-140
11	59	67	63	72	20-140
12	65	59	59	63	20-140
13	64	68	66	64	20-140
14	72	61	59	64	20-140
Combined Mean	66.5	61.5	63.3	65.8	
20	Change From Baseline		-6.1%	-3.4%	+0.005%

Level of Significance: p=0.0236

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TABLE VI
THE EFFECT OF NIASPAN® THERAPY ON URIC ACID LEVELS (mg/dL)
(1500 mgs dosed once-a-day at night)
(n = 28)

Weeks of Therapy With Niaspan®

Pt#	Baseline	2 Wks.	4 Wks.	8 Wks.	Reference Range
GROUP A					
1	5.2	5.0	4.8	4.3	4.0-8.5
2	4.0	4.6	4.5	6.2	2.5-7.5
3	6.3	7.0	6.5	6.2	4.0-8.5
4	3.1	4.6	4.2	3.8	2.5-7.5
5	3.4	NA	3.3	4.2	2.5-7.5
6	6.6	5.5	5.6	4.7	4.0-8.5
7	3.8	4.5	4.3	4.9	2.5-7.5
8	4.4	3.8	5.1	4.5	2.5-7.5
9	3.9	4.5	4.6	3.5	2.5-7.5
10	2.6	2.9	2.8	2.7	2.5-7.5
11	4.7	5.5	5.2	5.3	2.5-7.5
GROUP B					
1	3.7	4.2	4.7	3.5	2.5-7.5
2	2.8	3.5	3.6	2.3	4.0-8.5
3	4.2	5.3	5.5	5.3	2.5-7.5
4	4.7	3.9	5.1	3.6	4.0-8.5
5	3.7	4.1	4.1	3.8	2.5-7.5
6	PATIENT WITHDREW DUE TO FLUSHING				

7	5.8	6.6	6.6	6.8	2.5-7.5
8	4.7	4.3	5.4	5.6	2.5-7.5
9	3.7	4.6	5.1	3.8	2.5-7.5
10	4.2	5.0	4.4	8.5	2.5-7.5
11	1.9	3.0	2.8	5.0	2.5-7.5
12	5.6	5.4	6.2	5.6	4.0-8.5
13	4.2	4.6	4.6	5.3	2.5-7.5
14	5.5	5.4	6.1	5.3	2.5-7.5
Combined Mean	4.54	4.82	4.92	4.86	*p=0.3450
Change From Baseline		+6.2%	+8.4%	+7.0%	

*Level of Significance: p=0.3450

TABLE VII
THE EFFECT OF NIASPAN® THERAPY
ON FASTING GLUCOSE LEVELS (mg/dL)
(n = 28)

Weeks of Therapy With Niaspan®

<u>Pt#</u>	<u>Baseline</u>	<u>2 Wks</u>	<u>4 Wks.</u>	<u>8 Wks</u>	<u>Reference Range</u>
GROUP A					
1	114	122	123	110	70-115
2	101	105	107	101	80-125
3	99	98	103	103	70-115
4	100	118	94	94	80-125 80-12
5	89	NA	82	103	80-125
6	97	103	94	107	70-115
7	85	107	100	94	80-125

TABLE VII (Continued)

8	98	107	103	101	80-125
9	97	97	100	110	80-125
10	94	101	111	97	70-115
11	102	103	95	95	80-125
GROUP B					
1	101	97	83	99	70-115
2	90	95	96	89	80-125
3	96	98	95	97	70-115
4	116	139	113	125	80-125
5	88	98	91	95	70-115
6	PATIENT WITHDREW DUE TO FLUSHING				
7	106	114	118	117	70-115
8	95	106	106	108	70-115
9	81	92	84	92	70-115
10	108	117	122	105	70-115
11	85	106	106	108	70-115
12	92	89	101	86	80-125
13	99	105	94	100	70-125
14	100	108	84	107	70-125
Combined Mean	98.4	105.8	101.6	102.3	
Change From Baseline		+7.5%	+3.3%	+4.0%	
Level of Significance: p=0.0021					

In order to provide a comparison between the state of the art prior to the present invention, and in order to quantify the magnitude of the improvement that the invention provides over the prior art, another study was conducted. This study included 240 patients dosed according to the present

invention as described hereinabove. Compared to this group was the group of patients studied by McKenney *et al.*, as reported hereinabove. The results of this study are reported in TABLE VIII hereinbelow.

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TABLE VIII (Continued)
A Comparison of Changes in Liver Function Tests

		DOSE							
		0	500	1000	1500	2000	2500	3000	TOTAL
5	McKenney SR Niacin ^a								
	AST	23.8	27.9	40.4	36.6	56.5	NA	97.0	
	%	--	117	170	154	237	NA	408	
10	Invention Dosage ^c								
	AST	24.3	NA	23.7	17.5	26.6	27.6	27.8	
	%	--	NA	98	11398	109113	114	114	
15	McKenney SR Niacin								
	ALT	25.6	29.5	36.3	39.0	59.1	NA	100.0	
	%	--	115	142	152	231	NA	391	
20	Invention Dosage								
	ALT	21.4	NA	18.7	22.6	21.3	22.4	21.8	
	%	--	NA	87	106	100	105	102	
25	McKenney SR Niacin								
	ALK	95	95	106	105	136	NA	135	

		Invention Dosage				NA				142	
% ^a		100	112	111	143	NA		142			
ALK	74.7	NA	73.9	76.1	73.4						
%	--	NA	99	102	98						
McKenney SR Niacin											
Drop	--	0	2	2	7	NA	7	18			
n	--	--	--	--	--	--	--	23			
%	--	0	9	9	30	NA	30	78			
Invention Dosage											
Drop	--	--	0	0	0	0	0	0	0	0	
n	--	--	26	67	97	35	15	240			
%	--	--	0	0	0	0	0	0	0	0	
1 year	--	--	15	46	77	31	15	184			
1 year	--	--	58	69	79	89	100	77			

^a Dosed twice-per-day as described in "A Comparison of the Efficacy and Toxic Effects of Sustained - vs Immediate - Release Niacin in Hypercholesterolemic Patients" by McKenney et al. *Journal of the American Medical Association*, March 2, 1994; Vol. 271, No. 9, pages 672-677.

^b SR is "sustained release"

^c Dosed once-per-day at night

The results of the comparison of the studies reported in Table VIII show that the control group (the McKenney group) had 18 of 23, or 78 percent of the patients therein drop out of the test because of an increase in their respective liver function tests. The patients withdrew at the direction of the investigator. In comparison, a group of 240 patients treated according to the present invention had zero patients drop out, based upon the same criteria for withdrawal. The test results reported above indicate that this sustained release dosage form caused no elevation in liver function tests (i.e., no liver damage), no elevations in uric acid and only a small, 7.5% increase in fasting glucose levels which in fact decreased during continued therapy.

Thus it should be evident that the compositions and method of the present invention are highly effective in controlling hyperlipidemia in hyperlipidemics, by reducing the levels of LDL cholesterol, triglyceride and Lp(a) while increasing HDL cholesterol levels. The present invention is also demonstrated not to cause elevations in liver function tests, uric acid or glucose levels for the hyperlipidemics.

Based upon the foregoing disclosure, it should now be apparent that the use of the compositions and methods described herein will carry out the objects set forth hereinabove. It is, therefore, to be understood that any variations in sustained release formulation evident fall within the scope of the claimed invention and thus, the selection of specific component elements can be determined without departing from the spirit of the invention herein disclosed and described. In particular, sustained release excipients, binders and processing aids according to the present invention are not necessarily limited to those exemplified hereinabove. Thus, the scope of the invention shall include all modifications and variations that may fall within the scope of the attached claims.

Having described my invention, I claim:

(1) A method of treating a lipidemic disorder with a nicotinic acid formulation suitable for oral administration once-a-day as a single dose without causing drug-induced hepatotoxicity in an individual to a level which would require use of the nicotinic acid formulation to be discontinued by the individual, comprising:

orally administering to the individual once-a-day as a single dose an effective amount of an intermediate release nicotinic acid formulation without causing drug-induced hepatotoxicity in the individual to a level which would require use of the intermediate nicotinic acid formulation by the individual to be discontinued, the intermediate release nicotinic acid formulation having

a dissolution curve similarity fit factor F_2 of at least about 79, and

an *in vitro* dissolution profile, when measured in a type I dissolution apparatus (basket), according to U.S. Pharmacopeia XXII, at about 37°C in deionized water at about 100 rpm, as follows

(a) less than about 15% of the nicotinic acid is released after about 1 hour in the apparatus,

(b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours in the apparatus,

(c) between about 30% and about 45% of the nicotinic acid is released after about 6 hours in the apparatus,

(d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours in the apparatus,

(e) between about 50% and about 75% of the nicotinic acid is released after about 12 hours in the apparatus, and

(f) at least about 75% is released after about 20 hours in the apparatus.

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(2) A method of claim 1, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

(3) A method of claim 1, wherein the nicotinic acid formulation is a tablet.

5 (4) A method of claim 3, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg and about 750mg.

(5) A method of claim 1, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus;

(d) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% is released after about 20 hours in the apparatus.

20 (6) A method of claim 5, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

(7) A method of claim 5, wherein the nicotinic acid formulation is a tablet.

(8) A method of claim 7, wherein the tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg and about 750mg.

(9) A method of claim 1, wherein the *in vitro* dissolution profile is as follows:

5 (a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus;

(d) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% is released after about 20 hours in the apparatus.

10 (10) A method of claim 9, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

15 (11) A method of claim 9, wherein the nicotinic acid formulation is a tablet.

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(12) A method of claim 11, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg and about 750mg.

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(13) A method of claim 1, wherein the single dose is administered to the individual during the evening or at night.

(14) A method of claim 13, wherein the single dose is administered to the individual during the evening or at night between about 6pm and 12 am.

(15) A method of claim 13, wherein the single dose is administered to the individual during the evening or at night between about 8pm and 10pm.

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(16) A method of treating a lipidemic disorder with a nicotinic acid formulation suitable for oral administration once-a-day as a single dose without causing drug-induced hepatotoxicity in

20 an individual to a level which would require use of the nicotinic acid formulation to be discontinued by the individual, comprising:

25 orally administering to the individual once-a-day as a single dose an effective amount of an intermediate release nicotinic acid formulation without causing drug-induced hepatotoxicity in the individual to a level which would require use of the intermediate nicotinic acid formulation by the individual to be discontinued, the intermediate release nicotinic acid formulation containing at least about 1000 mg of nicotinic acid and having

a dissolution curve similarity fit factor F_2 of at least about 44, and
an *in vitro* dissolution profile, when measured in a type I dissolution apparatus (basket),
according to U.S. Pharmacopeia XXII, at about 37°C in deionized water at about 100 rpm, as
follows

5 (a) less than about 15% of the nicotinic acid is released after about 1 hour in the
apparatus,

10 (b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours
in the apparatus,

15 (c) between about 30% and about 45% of the nicotinic acid is released after about 6 hours
in the apparatus,

(d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours
in the apparatus,

(e) between about 50% and about 75% of the nicotinic acid is released after about 12
hours in the apparatus, and

(f) at least about 75% is released after about 20 hours in the apparatus.

20 (17) A method of claim 16, wherein approximately 100% of the nicotinic acid is released
after about 20 hours in the apparatus.

(18) A method of claim 16, wherein the nicotinic acid formulation is a tablet.

25 (19) A method of claim 16, wherein the *in vitro* dissolution profile is as follows:
(a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1
hour in the apparatus;
(b) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3
hours in the apparatus;

(c) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus;

(d) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus; and

5 (f) at least about 75% is released after about 20 hours in the apparatus.

(20) A method of claim 19, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

(21) A method of claim 19, wherein the nicotinic acid formulation is a tablet.

(22) A method of claim 1, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus;

20 (d) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% is released after about 20 hours in the apparatus.

(23) A method of claim 22 wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

(24) A method of claim 22, wherein the nicotinic acid formulation is a tablet.

5 (25) A method of claim 16, wherein the single dose is administered to the individual during the evening or at night.

(26) A method of claim 25, wherein the single dose is administered to the individual during the evening or at night between about 6pm and 12 am.

10 (27) A method of claim 25, wherein the single dose is administered to the individual during the evening or at night between about 8pm and 10pm.

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**METHODS FOR TREATING
HYPERLIPIDEMIA WITH INTERMEDIATE RELEASE NICOTINIC ACID
COMPOSITIONS HAVING UNIQUE BIOPHARMACEUTICAL CHARACTERISTICS**

5

Abstract

Methods for treating hyperlipidemia with intermediate release nicotinic acid formulations having unique biopharmaceutical characteristics, without causing drug-induced hepatotoxicity to a level which would require discontinuation of the therapy, are disclosed. According to the methods of the present invention, the intermediate nicotinic acid formulations are administered as a single dose once-a-day during the evening or at night. While the methods of the present invention contemplate administering the intermediate release nicotinic acid formulations at any time during a 24 hour period, it is preferable to administer them as a single dose during the evening or at night between about 6:00 pm. and 12:00 a.m., preferably between about 8:00 p.m. and 12:00 a.m., and most preferably between about 8:00 p.m. and 10:00 p.m.

FIGURE 1

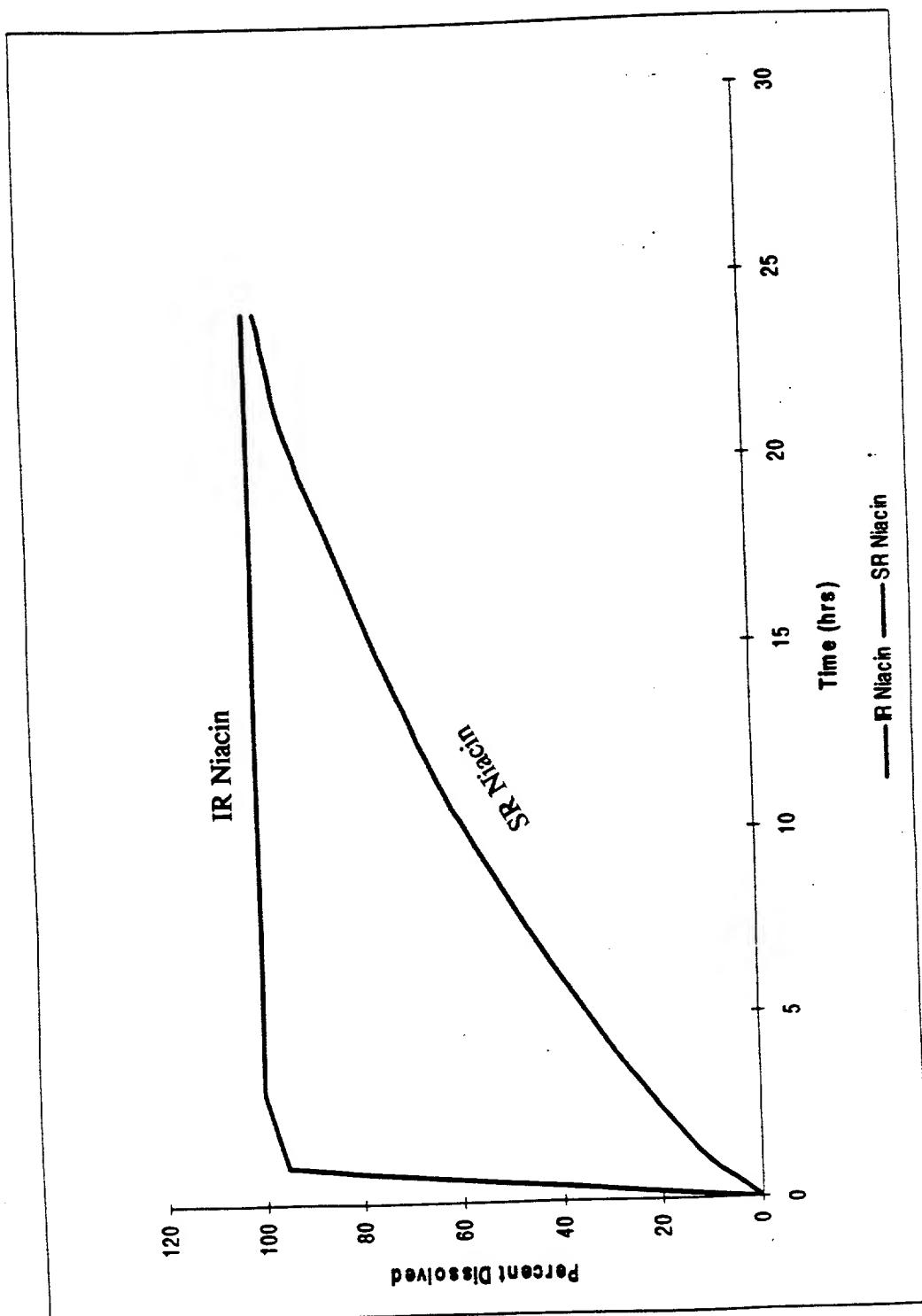
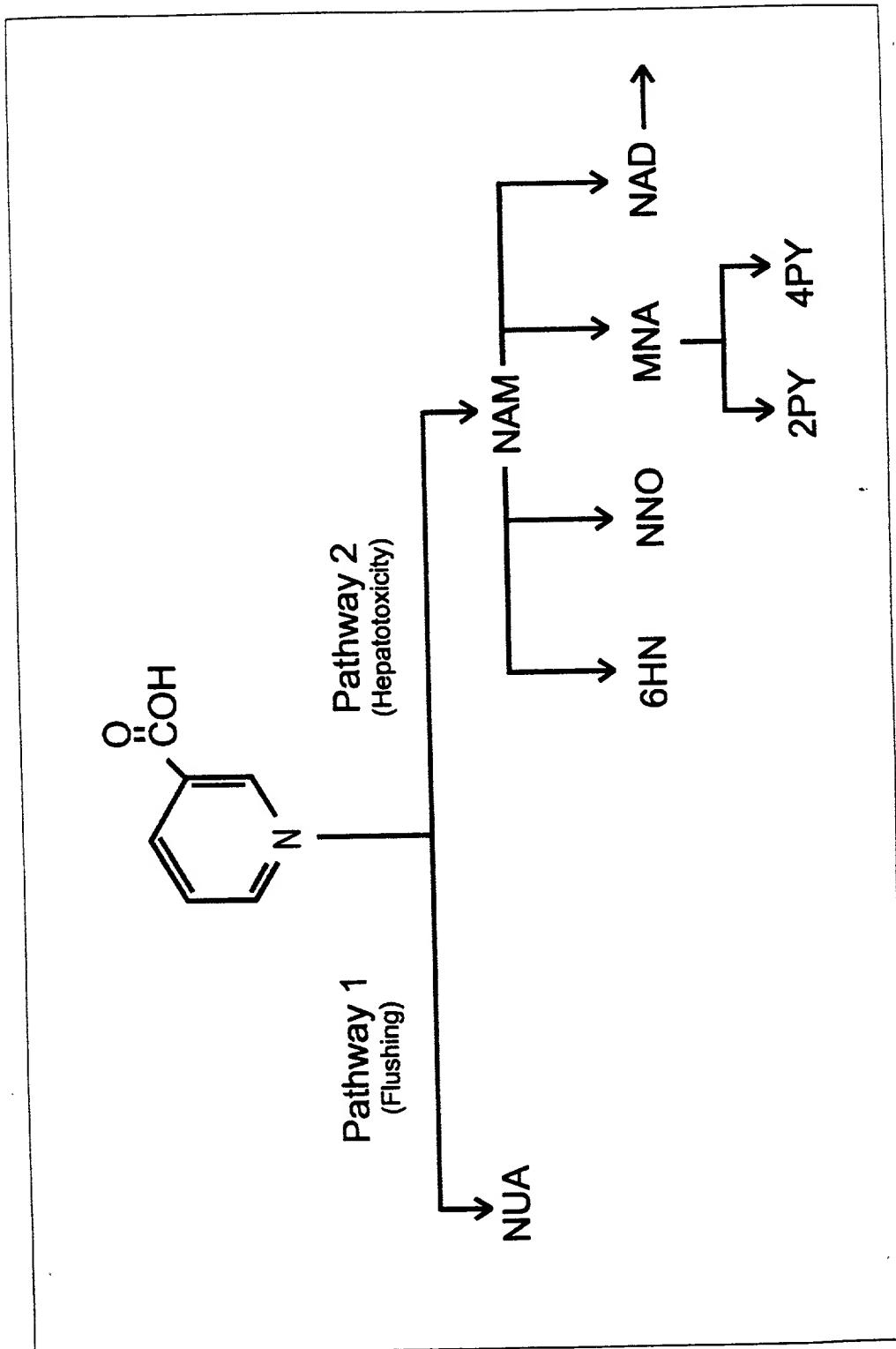


FIGURE 2



Wagner-Nelson Method

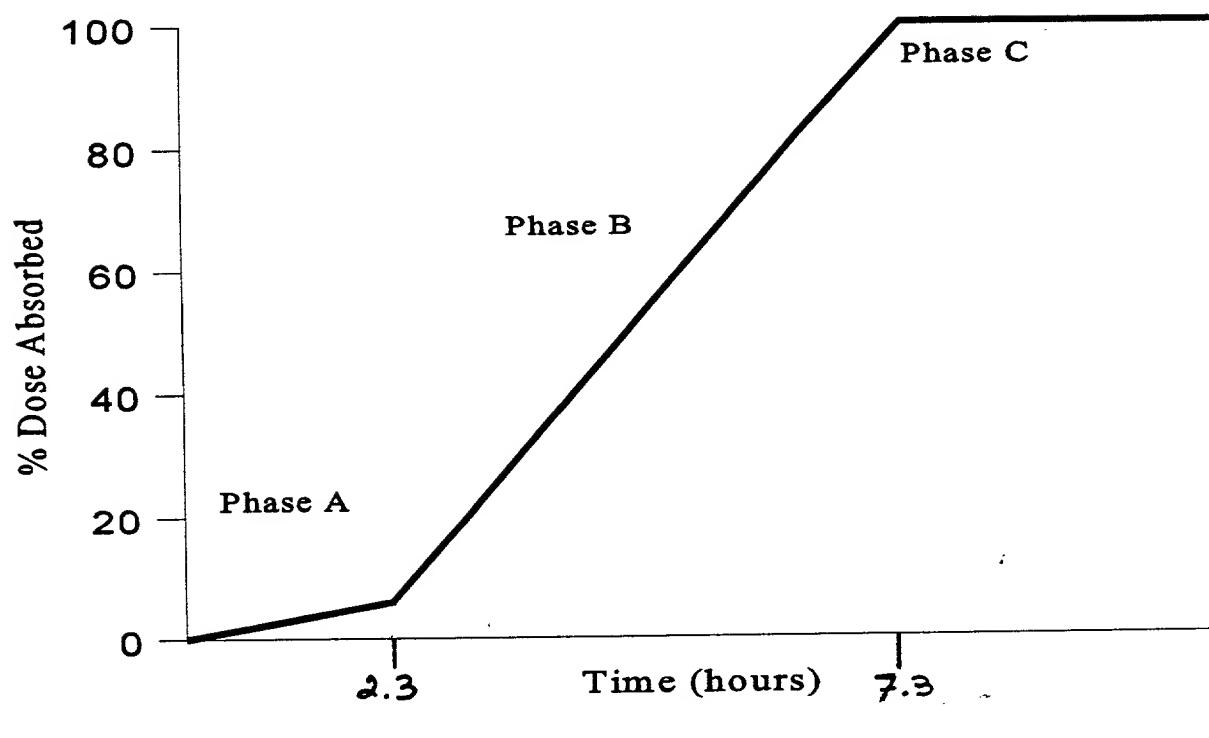


FIGURE 3

FIGURE 4

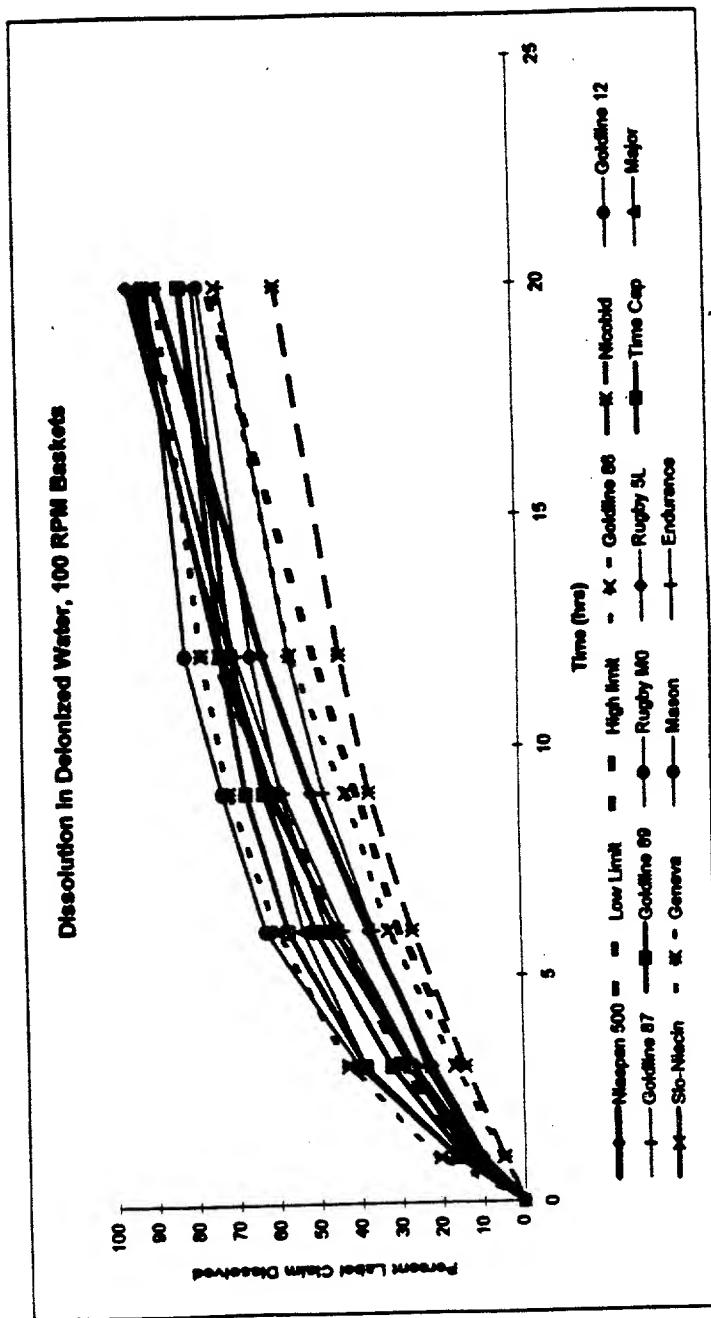
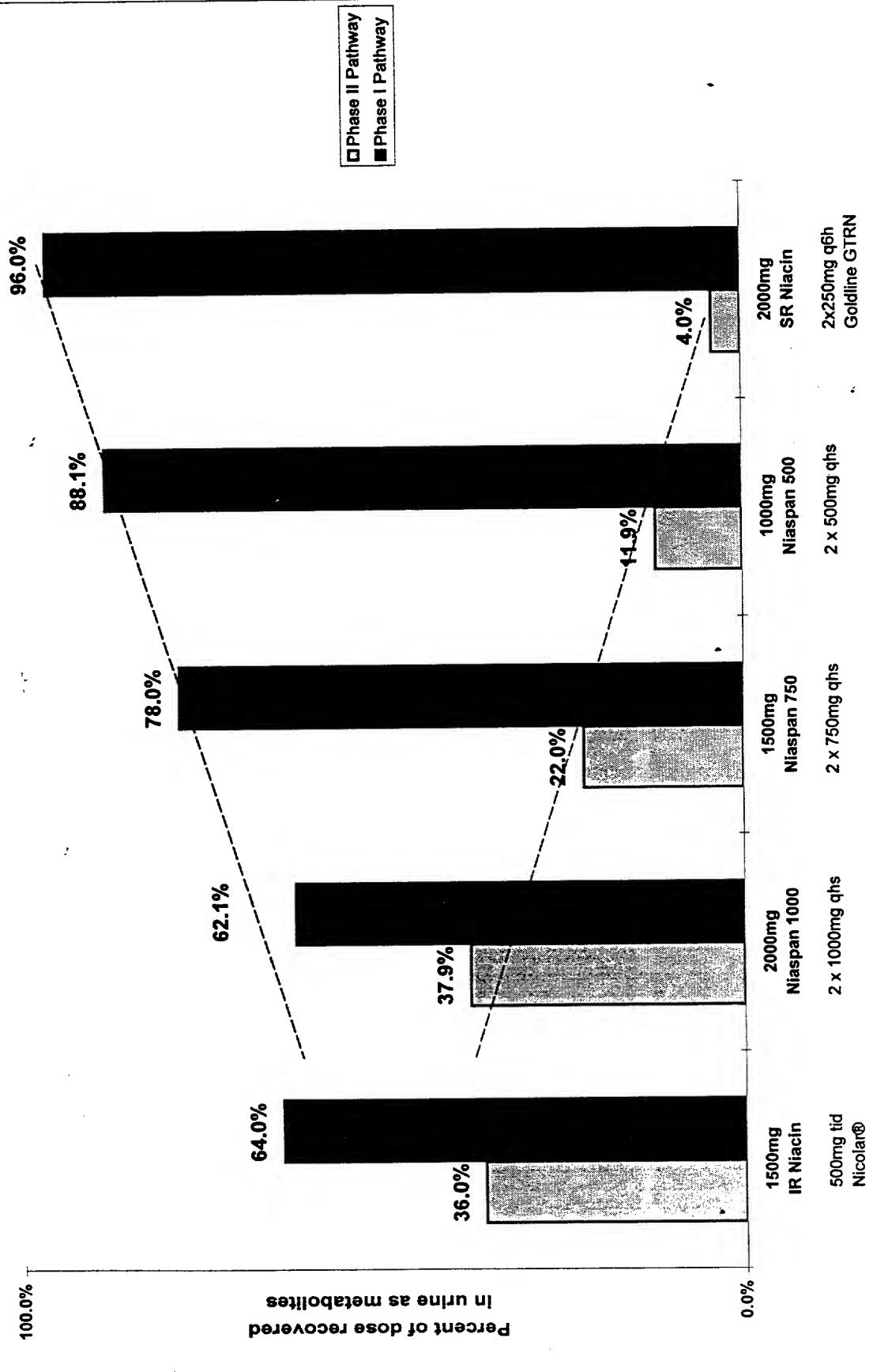


FIGURE 5

**Urine Recovery of Metabolites
Multiple-Dose Studies**



Express Mail No. EI637428686US

**DECLARATION FOR PATENT APPLICATION AND
POWER OF ATTORNEY**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I (we) believe we are the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled

**Methods for Treating Hyperlipidemia With Intermediate Release
Nicotinic Acid Compositions Having Unique Biopharmaceutical Characteristics**

the specification of which

(Check one)

X is attached hereto.

was filed on as Application Serial No. _____ and

was amended on (if applicable).

I (we) hereby state that we have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I (we) acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I (we) hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

			<u>Priority Claimed</u>	
<u>(Number)</u>	<u>(Country)</u>	<u>(Day/Month/Year Filed)</u>	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>

I (we) hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not

disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I (we) acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (Patented, Pending, Abandoned)
(Application Serial No.)	(Filing Date)	(Status) (Patented, Pending, Abandoned)

I (we) hereby appoint the following as our representative(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **PETER J. MANSO** (Reg. No. 32,264), **A. M. (ANDY) ARISMENDI, JR.** (Reg. No. 31,715), **JOHN R. KIRK, JR.** (Reg. No. 24,477), **GERALD T. WELCH** (Reg. No. 30,332), **C. PATRICK TURLEY** (Reg. No. 35,723), **LISA H. MEYERHOFF** (Reg. No. 36,869), **KEVIN R. HANSBRO** (Reg. No. 38,485), **ALAN R. THIELE** (Reg. No. 30,694).

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1445 Ross Avenue, Suite 1800
Dallas, Texas 75202-2799

I (we) hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor Eugenio A. Cefali

Inventor's signature _____

Date _____

Residence 5221 NW 78th Terrace

Citizenship USA

Post Office Address 5221 NW 78th Terrace

Applicant or Patentee: Eugenio A. Cefali Atty.Dkt. No.: 32892.19
Serial or Patent No.: Unassigned
Filed or Issued: Concurrently
For: Methods for Treating Hyperlipidemia With Intermediate Release Nicotinic Acid Compositions Having Unique Biopharmaceutical Characteristics

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

the owner of the small business concern identified below:
 an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN KOS Pharmaceuticals, Inc.

ADDRESS OF SMALL BUSINESS CONCERN 1001 South Bayshore Drive, Suite 2502, Miami, FL 33131

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled Methods for Treating Hyperlipidemia With Intermediate Release Nicotinic Acid Compositions Having Unique Biopharmaceutical Characteristics by the inventor(s) Eugenio A. Cefali described in

the specification filed herewith
 application serial no. _____, filed _____
 patent no. _____, issued _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____
ADDRESS _____
 INDIVIDUAL SMALL BUSINESS CONCERN NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Daniel M. Bell
TITLE OF PERSON OTHER THAN OWNER President
ADDRESS OF PERSON SIGNING 1001 South Bayshore Drive, Suite 2502, Miami, Florida 33131

SIGNATURE _____ DATE _____